Remarks/Arguments

Claims 119-126 and 129-131 were pending in this application and are rejected on various grounds. Claims 119-121 are hereby canceled without prejudice or disclaimer to pursue the canceled subject matter in subsequent continuation or divisional applications. Claims 122-123 have been amended to recite the functional recitation, "wherein said polypeptide enhances the uptake of glucose or FFA (free fatty acids) by adipocyte cells," support for which is found in the instant specification in Example 158, page 530, lines 13-15". No new matter is added by way of these amendments and their entry is respectfully requested.

Claim Rejections – 35 USC § 101/ 112, first paragraph

Claims 119-126 and 129-131 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-126 and 129-131 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

Rejections to the canceled claims 119-121 are hereby considered moot. Applicants traverse the rejections to the remaining claims.

The Examiner continues to maintain the rejections based on the gene amplification assay (see pages 3-6 of the Office Action). But, as indicated in their response filed January 20, 2006, instead of the gene amplification assay, the instantly pending claims were amended to rely upon assay 94 or 'the glucose/FFA uptake assay,' (Example 158) for patentable utility of PRO1182 polypeptides. Accordingly, any of the Examiner's rejections /references or discussions referring to the gene amplification assay are not currently addressed. Those rejections referring to the glucose/FFA uptake utility are discussed below.

Arguments

Previously, Applicants had erroneously referred to PRO1182 as a molecule that inhibits glucose/FFA uptake by adipocytes. In this response, Applicants have amended this error, and the

instant claims correctly recite that PRO1182 enhances glucose/ FFA uptake by adipocytes. Support for this amendment is clearly present in Example 158, which discloses the glucose/ FFA uptake assay as follows:

> Primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again.

As a control, identical incubations and samplings were performed on cells that were incubated overnight in media, initially supplemented with insulin rather than the PRO1182 polypeptide. Results were scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. As PRO1182 resulted in more than 1.5 times the uptake of the insulin control, PRO1182 tested positive as a **stimulator** of (or enhanced) glucose/FFA uptake in adipocyte cells (specifically, see Example 158).

Applicants had submitted supportive references, Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), to show that, the utility for agents modulating glucose/FFA uptake was well known in the art at the time of filing of the instant application, for instance, in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia. Therefore, one skilled in the art would have known how to use of PRO1182 in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia, based on the glucose/FFA uptake assay results for PRO1182.

In the recent Office action, the Examiner herself acknowledges the teachings of the articles by the Applicants, indicating that "each of the references cited by Applicants teaches that the agents utilized in the assays *enhance* glucose uptake.....**Disorders such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized by a reduction in the amount of glucose entering all cells, including adipocytes.....Therefore, as emphasized by Tafuri et al., Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), one**

skilled in the art is searching for agents that will enhance glucose uptake into adipocyte cells." (emphasis added; page 7, line 2 through page 8, line 2 of instant Office action).

Therefore, based on the instant results demonstrating the ability of the PRO1182 polypeptides to enhance glucose uptake in the glucose/ FFA assay, one skilled in the art, as the Examiner acknowledges, would readily recognize that PRO1182 polypeptides are usefulin the treatment of disorders benefiting from this biological activity, such as obesity, diabetes, or hyper- or hypo-insulinemia.

The Examiner also maintained the previous rejection that "Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000) teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification....None of the references utilizes the same grading scale disclosed in the instant specification, but instead report dose-response curves. The instant specification does not report any specific cell numbers or statistical differences and there is no indication in the specification as to how PRO1182 inhibited glucose uptake as compared to control or whether the results were significant" (Emphasis added). The Examiner concludes that the PRO1182 peptide is not in currently available form, and the asserted utility is not substantial. Applicants once again strongly disagree with the utility standards utilized by the Examiner in this rejection.

Applicants respectfully submit that, compliance with the utility requirement does not require that the methodology used in making the invention be the same as those used in the referenced or related art. What is important is that the assay be a well- recognized assay and that guidelines be provided in the specification to perform the assay, including assay read-out, if applicable. As discussed in their response dated January 20, 2006, Applicants submitted that the glucose uptake assay is a well-accepted assay in the art for identifying molecules that modulate glucose uptake. The fact remains that the results of the adipocyte glucose/FFA uptake assay were positive, indicating that PRO1182 polypeptides are useful in *enhancing* glucose uptake by adipocyte cells. The instant specification also clearly discusses the controls used in the assay. For example, the results of the glucose uptake assay were scored as positive if the uptake was greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. Since PRO1182 resulted in more than 1.5 times the uptake of the

insulin control, PRO1182 tested positive as a **stimulator** (or enhancer) of glucose/FFA uptake in adipocyte cells.

The Examiner's requirement for specific "cell numbers and statistical results" are also clearly not a requirement of the utility standards set by the USPTO. Applicants submit that the glucose uptake assay described herein is a comparative assay, meaning that the utility is based upon a comparison of relative uptake levels between a well-accepted and known control like insulin (for glucose uptake) and a test molecule like PRO1182. Useful pharmacological information is obtained when a relative difference is observed in this assay. In addition, the need for "cell numbers or statistical results" is a misplaced requirement, and is a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a pharmacological or diagnostic assay, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new assay, will indeed ask for actual numerical data, statistical analysis, and other specific information before any assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.

Accordingly, Applicants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility and in fact, based on the results of the glucose uptake assay, PRO1182 polypeptides are in currently available form, and the asserted utility is specific, credible and substantial. Therefore, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

Claim Rejections – 35 USC § 112, first paragraph- Written Description

Claims 119-123 stand rejected under 35 U.S.C. 112, first paragraph because, according to the Examiner, the subject matter was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing. Applicants respectfully traverse this rejection.

Rejections to canceled claims 119-121 are hereby considered moot. Applicants traverse the rejections to the remaining claims.

Arguments:

The legal standards for evaluating Written description were discussed in the previous response. Briefly, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains.

The currently amended claims claim the genus of polypeptides with at least 95-99% sequence identity to SEQ ID NO:357 with the functional recitation: "wherein said polypeptide enhances the uptake of glucose or FFA (free fatty acids) by adipocyte cells," which, as discussed above, is based on a well-established assay known to the skilled artisan at the effective filing date of this application. Moreover, the instant invention evidences the actual reduction to practice of full-length PRO1182 of SEQ ID NO: 357, with or without its signal sequence, or encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 203088. Therefore, the claimed polypeptides of Claims 122 and 123 are defined both by functional as well as structural features.

The present situation is analogous to Example 14 on pages 53-55 of the Written Description Training Materials which analyzes a claim directed to a protein and variants thereof having 95% sequence identity, all of which share the same biological function, for its compliance with the written description requirement of 35 U.S.C. §112, first paragraph. The Written Description Training Materials conclude that such a claim satisfies the written description requirement of 35 U.S.C. §112, first paragraph, when: (1) a single protein sequence is actually reduced to practice, (2) procedures for making variants of that "reduced to practice" protein sequence are conventional in the art, and (3) an assay is described which allows identification of other proteins having the same biological activity. The reasoning provided by the USPTO in the Written Description Training Materials is that:

"[t]here is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO:...does not have substantial variation since all of the variants must possess the specified [biological function] and must have at least 95% identity to the reference sequence, SEQ ID NO:...The single species disclosed ***is representative of the genus*** because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:...which are capable of the specified [biological function]. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by members of the genus.....{As such], the disclosure meets the requirements of 35 U.S.C. § 112, first paragraph, as providing adequate written description for the claimed invention." (emphasis added).

The instantly pending claims recite polypeptides having 95% or 99% sequence identity with the disclosed polypeptide sequence SEQ ID NO: 357, and also include the functional recitation: "wherein said polypeptide enhances the uptake of glucose or FFA (free fatty acids) by adipocyte cells." Example 158, (page 530) of the present application provides detailed protocols for the glucose or FFA (free fatty acids) uptake assay by adipocyte cells including the extensive step-by-step guidance in the specification. Applicants claim only those proteins which meet both recitations of the claims, structural and functional. The specification further describes methods for the determination of percent identity between two amino acid sequences. In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention (page 306-308, line 14 onwards). The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 372, line 36 to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, one of skill in the art could identify whether a variant PRO1182 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence is identified, the specification sets forth methods for making the amino acid sequences (see page 305, line 23 and page 371) and methods of preparing the PRO polypeptides (Example 140-143, page 376).

Based on the detailed description of the cloning and expression of variants of 1182 in the specification, the description of the glucose or FFA (free fatty acids) uptake assay, the description of testing for variant polypeptides in the assay, the actual reduction to practice of sequence SEQ ID NO:357 and the functional recitation in the instant claims, one of skilled in the art would

know that Applicants possessed the invention as claimed in the instant claims, at the time of filing of the application. From the specific activity of the claimed polypeptide, the description of the claimed genus is achieved.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this outstanding rejection under 35 U.S.C. §112, first paragraph.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney Docket No.: **39780-2730P1C33**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 10,2006

Ginger R. Dreger, Esq.
Reg. No. 33,055

HELLER EHRMAN, LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

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8/10/06 9:38 AM (39780.2730)